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Remifentanil Induces Systemic Arterial Vasodilation in Humans with a Total Artificial Heart

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Background: **To assess intrinsic vascular effects of remifentanil, increased concentrations were infused in critically ill patients with a total artificial heart.**

Methods: **In the early postoperative period after implantation of a total artificial heart, nine ventilated patients requiring short general anesthesia were included in this study. After anesthesia was induced with 0.3 mg/kg intravenous etomidate, the artificial heart settings were modified to render cardiac output "preload-independent." While maintenance of anesthesia was ensured by a continuous infusion of etomidate, increased concentrations of remifentanil (from 0.1 to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were infused in steps of 5 min under hemodynamic monitoring, including left and right atrial pressures, systemic and pulmonary arterial pressures, and left and right cardiac indices. The invasive procedure was started under the highest concentration of remifentanil tolerated by the patient. Infusion of remifentanil was stopped at the end of the invasive procedure, while etomidate infusion was maintained. New hemodynamic measurements were performed at the end of the 12-min recovery period.**

Results: **Remifentanil produced a dose-dependent and significant decrease in systemic arterial pressure and vascular resistances (n = 9) from a concentration of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. No significant changes were observed on pulmonary vascular resistances (n = 6). Neither right (n = 9) nor left (n = 6) atrial pressures were affected by remifentanil infusion. Hemodynamic variables returned to baseline value over the 12-min recovery period.**

Conclusions: **In humans with a total artificial heart, remifentanil induces a systemic arterial vasodilation without significant effect on the capacitance vessels.**

REMIFENTANIL is a potent μ-opioid receptor agonist with attractive pharmacokinetic properties.[1] It has been proposed by some cardiac anesthesiologists as an agent of choice for patients undergoing fast-track cardiac surgery.[2–4] Although remifentanil is now clinically widely used in cardiac surgical patients,[2–8] some studies have indicated that this opioid may be associated to significant hemodynamic changes.[9–12] These hemodynamic changes are characterized by decreases in arterial pressure, heart rate, cardiac output, and systemic vascular resistance.[10–12] Unfortunately, little information is available in the literature regarding the mechanism behind the hypotensive effect of remifentanil. In isolated human right atrial trabeculae, remifentanil impairs neither inotropic nor lusitropic properties of the myocardium.[13] However, Unlügenc *et al.*[14] reported that remifentanil induces vasorelaxation in isolated rat thoracic aorta by an endothelium-dependent mechanism. Although useful, these *in vitro* studies present serious limitations. As previously reported by our group,[15–17] the implantation of an artificial heart as a bridge to cardiac transplantation in patients with end-stage cardiac failure offers an unique opportunity to assess the intrinsic peripheral vascular effects of anesthetic drugs independently of their myocardial influences in humans. Therefore, we evaluated intrinsic vascular effects of remifentanil in critically ill patients in the early postoperative period after implantation of a CardioWest (CardioWest Technologies Inc., Tucson, AZ) total artificial heart and in whom short general anesthesia was required for an invasive procedure.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

Patients

The study was conducted at the Institute of Cardiology in the Pitié-Salpêtrière Hospital (Paris, France) from December 2001 to August 2003 and was approved by our institutional medical ethics committee. Because care of patients conformed to standard procedures currently used in our cardiac intensive care unit, authorization was granted to waive informed consent for the study. We studied nine adult male patients who were admitted to the cardiac intensive care unit after implantation of the CardioWest total artificial heart. The total artificial heart was implanted in these patients because of the rapid onset of terminal congestive heart failure. In six patients, terminal cardiac failure resulted from dilated cardiomyopathy. In two patients, acute cardiac failure was related to a massive myocardial infarction. The remaining patient experienced severe hypertrophic cardiomyopathy. Because these patients were critically ill, they were systematically admitted to our cardiac intensive care unit after implantation of the total artificial heart. Mechanical ventilation with standard variables (controlled assisted

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ventilation, end-tidal volume 8 ml/kg, respiratory rate 14 min^{-1}, inspired oxygen fraction 60%, end expiratory pressure 0 cm H_2O, and inspiratory time ratio 33%) was required in the early postoperative period because pulmonary edema frequently persists for a few days.

In the early postoperative period, short general anesthesia may be required to perform invasive procedures in these critically ill patients. Because the sedation used in our cardiac intensive care unit is normally based on midazolam (50–100 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and morphine (30–60 $\mu g \cdot kg^{-1} \cdot h^{-1}$), a switch to a short general anesthetic technique using etomidate and remifentanil was required. Etomidate was chosen because our group previously showed that this hypnotic agent is devoid of significant hemodynamic effect in patients with a total artificial heart.[15] On the other hand, remifentanil was chosen for its short-acting pharmacokinetic profile.[1] As soon as the decision to perform the invasive procedure was taken, midazolam and morphine were immediately stopped, and thus, none of the nine patients received any sedative drugs during the 4 h preceding the remifentanil infusion. During the study, depth of anesthesia was assessed by using a noninvasive BIS® monitor (BIS® XP; Aspect Medical Systems, Natick, MA).

Hemodynamic monitoring included central venous and radial arterial catheters, which were inserted percutaneously by anesthesiologists, whereas pulmonary arterial and left atrial catheters were inserted intraoperatively by surgeons. For surgical technical reasons, pulmonary and left atrial catheters were only inserted in six patients (patients 3, 4, 5, 6, 8, and 9). The following hemodynamic variables were continuously monitored: systemic arterial pressures (systolic, mean, and diastolic), right and left atrial pressures, and pulmonary arterial pressures (systolic, mean, and diastolic). Left and right cardiac indices were calculated by the cardiac diagnostic unit of the Utah heart drive console, and the systemic and pulmonary vascular resistances were calculated by using standard formulae. Patients were not eligible for this study if high doses of norepinephrine ($> 0.5 \mu g \cdot kg^{-1} \cdot min^{-1}$) and/or epinephrine ($> 0.1 \mu g \cdot kg^{-1} \cdot min^{-1}$) were required to maintain arterial pressure.

The CardioWest Total Artificial Heart

A 70 ml-CardioWest total artificial heart was implanted as a bridge to transplantation because the patients had a rapid deterioration of hemodynamic status. Function of the artificial ventricles was continuously monitored by the cardiac output diagnostic unit of the Utah drive console, which calculates right and left cardiac output by multiplying right and left end-diastolic volumes (obtained from the diastolic area of the exhaust airflow under the curve of each ventricle) with heart rate. End-diastolic volume was measured by a flow transducer attached to the exhaust port of each drive system. The bias and precision of the cardiac output measurement by the Utah heart drive console have been estimated as being 2 and 7%, respectively.[17] The CardioWest total artificial heart settings included heart rate, drive pressures of the ventricles, systolic duration as a percentage of the cardiac cycle, and vacuum. The settings recommended by the manufacturer result in incomplete filling of the ventricular chamber (75–80%) as a result of adequate diastolic duration and heart rate; therefore, complete ventricular ejection must be achieved using an appropriate driving pressure. With these CardioWest settings, any decrease in atrial pressures further reduces end-diastolic ventricular volume, also reducing cardiac output, which is the product of heart rate (fixed) and end-diastolic ventricular volume (variable, according to atrial pressure). As previously reported,[15–17] the CardioWest settings can be modified so that the calculated cardiac output becomes "preload-independent." Briefly, by decreasing both heart rate and systolic duration, diastolic duration is significantly increased. Under these conditions, the ventricular chamber is always fully filled before the end of the time allocated to diastolic filling, and end-diastolic volume reaches its maximum value, 70 ml. A decrease in atrial pressure is not associated with a reduction in cardiac output, as long as the ventricular chamber remains completely filled at the end of diastole. Consequently, any change observed in hemodynamic pressures is only related to a change in the vascular tone within the corresponding vascular bed. The fact that the ventricular chamber was completely filled at the end-diastolic period was confirmed by a rapid fall of the flow curves on the Utah drive. As previously reported,[17] we have verified that these changes do not induce any significant hemodynamic effects (data not shown).

Experimental Protocol

The nine patients included in our study required short general anesthesia to perform an invasive procedure in the early postoperative period. After anesthesia was induced with intravenous bolus of etomidate (0.3 mg/kg), a continuous infusion (0.5–1 $mg \cdot kg^{-1} \cdot h^{-1}$) was started to maintain a bispectral value between 40 and 50 throughout the study. The artificial heart settings were modified to render the cardiac output preload-independent. After a brief equilibration period and measurements of baseline hemodynamic variables, increased intravenous doses of remifentanil (0.1, 0.25, 0.5, 0.75, and 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were infused under hemodynamic monitoring. Each dose of remifentanil was maintained during a step of 5 min, and all hemodynamic parameters were recorded at the end of each 5-min step. The increase in remifentanil infusion was stopped as soon as systolic arterial pressure decreased below 80 mmHg; no nociceptive stimuli were performed before reaching the highest concentration. The invasive procedure was started under the highest concentration of remifentanil

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Table 1. Clinical Characteristics of the Nine Patients Studied

Patient No.	Body Surface Area, m^2	Delay between Implantation of CardioWest and Study, days	Invasive Procedure Necessitating Analgesia	Days with Implant	Outcome
1	1.90	4	Transesophageal echocardiography	55	Survived
2	2.08	2	Central venous catheter	79	Survived
3	1.77	5	Drive line cleaning	28	Survived
4	2.37	3	Central venous catheter	62	Survived
5	1.73	2	Central venous catheter	42	Survived
6	1.78	2	Transesophageal echocardiography	20	Died
7	2.02	2	Drive line cleaning	110	Survived
8	1.98	3	Drive line cleaning	23	Survived
9	1.96	2	Transesophageal echocardiography	Ongoing (330)	Survived

tolerated by the patient. After termination of the invasive procedure, infusion of remifentanil was stopped. To confirm that cardiovascular changes were related to remifentanil infusion, new hemodynamic measurements were performed at the end of a 12-min recovery period, a time corresponding to four consecutive context-sensitive half-lives of remifentanil.[18] Because dyscapnia can significantly affect vasoregulation, blood gas analysis was performed before to start of remifentanil infusion to control the acid–base state of patients.

Statistical Analysis

Data are expressed as mean ± SD. Comparison of several means was performed with use of repeated-measures analysis of variance and the Newman-Keuls test. A P value less than 0.05 was required to reject the null hypothesis. All analyses were performed with use of NCSS 6.0 software (Statistical Solutions Ltd., Cork, Ireland) on a personal computer.

Results

The clinical characteristics of the patients are presented in table 1. The mean age of the nine patients studied was 35 ± 16 yr (range, 21–63 yr). Two patients required small doses of norepinephrine, which were maintained throughout the study (patient 1, 0.17 $\mu g \cdot kg^{-1} \cdot min^{-1}$; patient 6, 0.30 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Blood gas analysis showed the following values: pH, 7.46 ± 0.09; $Paco_2$, 33 ± 7 mmHg; HCO_3^-, 23.4 ± 3.7 mmol/l. The intravenous bolus of etomidate induced a significant decrease in the Bispectral Index values from 91 ± 11 to 41 ± 10 ($P < 0.05$). Subsequently, the Bispectral Index values remained stable throughout the study (range, 34–52). As expected, the changes of CardioWest settings induced no significant effect on cardiac indices (left: 3.1 ± 0.4 *vs.* 3.1 ± 0.4 $l \cdot min^{-1} \cdot m^{-2}$, not significant [NS]; right: 3.3 ± 0.4 *vs.* 3.2 ± 0.34 $l \cdot min^{-1} \cdot m^{-2}$, NS) and atrial pressures (left: 16 ± 8 *vs.* 11 ± 7 mmHg, NS; right: 16 ± 5 *vs.* 14 ± 5 mmHg, NS). The total artificial heart settings used during remifentanil infusion are summarized in table 2. No infusion of remifentanil necessitated early termination as a result of an adverse hemodynamic event. We observed no cutaneous or bronchial adverse effects. Consequently, the invasive procedure was performed in all nine patients under a continuous remifentanil infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

As expected, both right and left cardiac indices remained unchanged throughout the study (tables 3 and 4). In the systemic circulation, increased concentrations of remifentanil induced a significant decrease in systemic arterial pressure (table 3). Remifentanil produced a significant dose-dependent decrease in calculated indexed systemic vascular resistances of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (table 3). In the pulmonary circulation, remifentanil showed no significant effect on arterial pressure and indexed vascular resistances (table 4). Right and left atrial pressures were not significantly affected by increased concentrations of remifentanil (tables 3 and 4). After the termination of remifentanil infusion, a return to baseline values was obtained for all hemodynamic variables over the 12-min recovery period (tables 3 and 4).

Because the use of norepinephrine in two patients could have affected their vascular responsiveness, we also analyzed the vascular effect of increased doses of remifentanil in a subgroup excluding these two patients (n = 7). At the highest intravenous dose (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the decreases in systemic and pulmonary vascular resistances were 71 ± 9% of baseline ($P < 0.05$) and 94 ± 13% of baseline (NS), respectively. Neither right

Table 2. CardioWest Total Artificial Heart Settings Used during the Study

Patient No.	Heart Rate, beats/min	Systolic Duration, %	Left Drive Pressure, mmHg	Right Drive Pressure, mmHg
1	95	45	200	60
2	90	45	200	65
3	90	40	200	60
4	100	46	200	70
5	90	45	200	60
6	92	45	205	60
7	99	47	180	90
8	95	45	210	60
9	90	40	210	80

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Table 3. Baseline Values and Effects of Remifentanil on Systemic Circulation (n = 9)

Systemic Circulation Variable	Baseline Value	Concentration of Remifentanil (% of Baseline Value), $\mu g \cdot kg^{-1} \cdot min^{-1}$					
		0.1	0.25	0.5	0.75	1	Recovery
Left CI, $l \cdot min^{-1} \cdot m^{-2}$	3.1 ± 0.4	100 ± 1	99 ± 1	99 ± 2	99 ± 2	99 ± 2	101 ± 2
SAP, mmHg	115 ± 14	98 ± 5	92 ± 7	85 ± 10*	81 ± 12*	78 ± 14*	100 ± 3
DAP, mmHg	52 ± 13	94 ± 9	87 ± 8*	80 ± 9*	78 ± 10*	77 ± 11*	96 ± 8
MAP, mmHg	69 ± 16	95 ± 7	88 ± 6*	82 ± 7*	79 ± 7*	77 ± 9*	98 ± 6
RAP, mmHg	14 ± 5	93 ± 9	92 ± 15	92 ± 20	92 ± 22	92 ± 22	102 ± 19
SVR, $dyn \cdot s \cdot cm^{-5}$	1,459 ± 330	96 ± 9	89 ± 8*	80 ± 7*	77 ± 8*	74 ± 10*	100 ± 8

Data are presented as mean ± SD.

* $P < 0.05$ *vs.* baseline value.

CI = cardiac index; DAP = diastolic arterial pressure; MAP = mean arterial pressure; RAP = right atrial pressure; SAP = systolic arterial pressure; SVR = systemic vascular resistance.

nor left atrial pressure was significantly affected by the remifentanil infusion in this subgroup (data not shown).

Discussion

The principal findings of the current study are that remifentanil (1) provokes systemic arterial vasodilatation, (2) remains without significant effect on the capacitance vessels, and (3) does not significantly affect pulmonary arterial vascular tone in critically ill patients with a total artificial heart in which cardiac output is preload-independent. These systemic changes are rapidly reversible 12 min after termination of infusion of remifentanil.

Because of its potency and ultrashort pharmacokinetic profile, remifentanil has been proposed by some authors as an ideal opioid for patients with coronary artery disease.[2–8,19] Nevertheless, some clinical studies have reported that this opioid can induce significant cardiovascular disturbances that are potentially deleterious in coronary patients.[9–12] This hemodynamic instability includes a decrease in systemic vascular resistances and cardiac output that is thought to be related to a decrease of both stroke volume and heart rate.[10,12,20] Although these results have been confirmed in an experimental study in dogs,[20] few data are now available about the intrinsic mechanism of remifentanil-induced cardiovascular depression. The hypothesis of histamine release induced by administration of remifentanil (up to 30 μg/kg) has been ruled out in a clinical study.[11] We did not measure histamine levels, but it should be pointed out that we did not obverse any cutaneous or bronchial adverse effects. However, a recent *in vitro* study[14] showed that remifentanil produces significant direct smooth muscle relaxation in isolated thoracic aorta strips. These authors[14] reported that remifentanil-induced vasorelaxation is both endothelium-dependent and endothelium-independent, involving nitric oxide release and voltage-sensitive Ca^{2+} channel inhibition, respectively. Although the conditions of these *in vitro* studies differ considerably from clinical conditions, the results suggest that an intrinsic peripheral vascular effect may be involved in cardiovascular disturbances observed clinically. The benefit of the implantation of a CardioWest total artificial heart, as a bridge to cardiac transplantation, in patients with prelethal heart failure has been demonstrated previously.[21,22] Because these patients are critically ill during the immediate postoperative period, anesthesiologists in the intensive care unit may have to induce general anesthesia in these patients to allow invasive procedures. Therefore, implantation of the total artificial heart offers a unique opportunity to evaluate intrinsic vascular effect of drugs by eliminating myocardial interference.[15–17] By modifying the recommended settings (decrease in heart rate and systolic

Table 4. Baseline Values and Effects of Remifentanil on Pulmonary Circulation (n = 6)

Pulmonary Circulation Variables	Baseline Value	Concentration of Remifentanil (% of Baseline Value), $\mu g \cdot kg^{-1} \cdot min^{-1}$					
		0.1	0.25	0.5	0.75	1	Recovery
Right CI, $l \cdot min^{-1} \cdot m^{-2}$	3.2 ± 0.3	99 ± 1	97 ± 1	97 ± 3	98 ± 3	97 ± 3	99 ± 3
PAP systolic, mmHg	38 ± 8	97 ± 7	92 ± 5	90 ± 9	88 ± 9	86 ± 10	91 ± 6
PAP diastolic, mmHg	17 ± 7	96 ± 26	89 ± 20	91 ± 29	87 ± 25	87 ± 29	97 ± 28
MPAP, mmHg	23 ± 5	99 ± 12	92 ± 5	94 ± 17	87 ± 13	88 ± 13	99 ± 4
LAP, mmHg	11 ± 7	93 ± 11	89 ± 15	86 ± 20	86 ± 17	93 ± 23	105 ± 16
PVR, $dyn \cdot s \cdot cm^{-5}$	303 ± 113	104 ± 12	102 ± 12	105 ± 22	94 ± 14	95 ± 12	98 ± 8

Data are presented as mean ± SD.

* No significant difference *vs.* baseline value.

CI = cardiac index; LAP = left atrial pressure; MPAP = mean pulmonary arterial pressure; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

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duration), cardiac output becomes preload-independent and afterload-independent. Because the decrease in heart rate is compensated for by an increase in end-diastolic volume,[15–17] cardiac output is not affected by these new settings.

In our study, we tested increased concentrations of remifentanil from 0.1 to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. These ranges are currently used during cardiac surgery[2,4,7,12] and even during general surgery.[23] In the current study, remifentanil provoked a dose-dependent decrease in mean arterial pressure and systemic vascular resistances, with maximal decreases of 23 ± 9 and 26 ± 10%, respectively. Our results are consistent with those previously reported by different authors in patients undergoing coronary bypass grafting during anesthesia based on propofol and remifentanil.[10,12] Remifentanil did not induce significant effects on right and left atrial pressures in patients with a total artificial heart in which cardiac output was preload-independent. These findings suggest that remifentanil is devoid of significant effects on capacitance vessels. Although *in vivo* the cardiovascular changes of remifentanil are the result of myocardial and peripheral vascular effects, our results are consistent with those of Elliott *et al.*,[12] who found that central venous pressure and pulmonary capillary wedge pressure were not significantly modified by increased concentrations from 0.2 to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in cardiac surgical patients. In addition, the absence of a significant effect of remifentanil on venous return has been previously reported in an *in vivo* study in dogs.[20] This finding should be taken into account for the management of decreasing blood pressure effect of remifentanil. During our study, we observed that remifentanil induced no significant effect on pulmonary arterial vascular tone. Because we studied only six patients, we cannot absolutely eliminate an intrinsic pulmonary arterial effect of remifentanil. However, this result represents an interesting finding that must be taken into account during the anesthetic management of cardiac surgical patients with pulmonary hypertension.

To confirm that hemodynamic changes observed during short general anesthesia were related to the remifentanil infusion, we measured new hemodynamic parameters at a time equal to four consecutive context-sensitive half-lives. This half-life was previously found to be 3 min.[18] The return to baseline value of all hemodynamic parameters over the 12-min recovery period confirmed that cardiovascular changes were only related to remifentanil infusion.

The following points must be considered in the assessment of the clinical relevance of our study. First, the current study was conducted in critically ill patients who were highly stressed and had a long history of cardiovascular disease that almost certainly had altered their vascular responsiveness. Therefore, we cannot exclude that vascular effects of remifentanil could be different from those observed in healthy surgical patients. In addition, two of our nine patients required low-dose norepinephrine to maintain arterial pressure. Although the inclusion of these patients does not seem to affect our results, we cannot exclude that the use of norepinephrine might have underestimated the systemic vascular effect of remifentanil. Second, no hemodynamic pressures were recorded under zero-flow conditions. Consequently, calculated systemic vascular resistances did not take into account the waterfall phenomenon. Because assessing this phenomenon necessitates briefly disconnecting the drive lines,[16,17] for ethical reasons, it was not possible for us to measure the true downstream pressure of the arterial compartment of our patients. Consequently, the absolute values of systemic vascular resistances are probably overestimated by the standard formulae. This problem does not seem to apply to the pulmonary circulation because pulmonary arteries are characterized by a zero-flow pressure less than the pressure within pulmonary veins.[16,17] However, we do not think that this point interferes with the changes in systemic vascular resistances observed during remifentanil infusion because our results are expressed as percentage of baseline. Third, patients with a total artificial heart frequently have normal basic physiologic function including feeding and cycling after tracheal extubation. Nevertheless, we cannot exclude that the implantation of artificial hearts modifies vascular responses to vasodilator agents. Fourth, we reported that remifentanil is devoid of significant effect on pulmonary circulation. Because the number of patients was small (n = 6), the power of our analysis was low, and a moderate effect of remifentanil on pulmonary circulation cannot be completely ruled out. Fifth, our results are purely observational and do not allow us to assess the mechanism of arterial vasodilation of remifentanil.

In conclusion, in patients with a total artificial heart in which cardiac output is preload-independent, remifentanil induces a dose-dependent and significant systemic arterial vasodilation but remains without effect on pulmonary arteries. In addition, remifentanil is devoid of significant effects on capacitance vessels. Although our results were obtained in critically ill patients, this observational study suggests that systemic arterial vasorelaxation is involved in remifentanil-induced cardiovascular disturbances.

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